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Hidradenoma Papilliferum: A Clinicopathologic Study of 264 Tumors From 261 Patients, With Emphasis on Mammary-Type Alterations

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Key Words: hidradenoma papilliferum, anogenital mammary-like glands, vulva, skin, sclerosing adenosis, extramammary Paget disease

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INTRODUCTION

Hidradenoma papilliferum (HP), also known as papillary hidradenoma, is the most common benign lesion of female anogenital area derived from anogenital mammary-like glands (AGMLG). The latter are a normal constituent of the anogenital area.[1–5] Lesions affecting AGMLG are histopathologically very similar, if not identical, to those seen in the breast.[6–8] HP can be viewed conceptually as the cutaneous counterpart of mammary intraductal papilloma.[9–12] Previous case reports and case series demonstrated a number of metaplastic and hyperplastic changes in HP and demonstrated a relationship to AGMLG, but no systemic study on the morphological spectrum of this neoplasm has been performed. In this report, we present a histopathological study of 264 cases of HP, detailing various changes in the tumor and adjacent AGMLG, with emphasis on mammary-type alterations.

MATERIAL AND METHODS

Case Inclusion/Exclusion

A search in the consultation and routine institutional files of the authors between 1993 and 2015 years yielded 272 cases coded as HP involving the anogenital area. Hematoxylin–eosin-stained slides were reviewed to confirm the diagnosis. The histopathological findings were correlated with the clinical data to confirm the location and appropriate clinicopathological context. Eight cases were excluded (3 fibroadenomas, 2 syringocystadenoma papillifera, 1 vulvar lesion having features of mammary-type fibrocystic disease). Also, excluded was a case showing mixed features of fibroadenoma, and HP and another previously published HP with a ductal in situ carcinoma component.[13] Thus, 264 tumors from 261 patients were included in the study.

TABLE 1. Age Distribution of Patients With HP

Age Group, yr*	No. Cases (%)
20–29	14 (5.7)
30–39	46 (18.5)
40–49	70 (28.2)
50–59	62 (25)
60–69	34 (13.7)
70–79	20 (8.1)
80–89	2 (0.7)

*At the time of HP excision.

TABLE 2. Distribution of HP in the Anogenital Area

Location (n = 264)	No. Cases
Vulva, NOS	100
Labium major	48
Labium minus	26
Sulcus interlabialis	9
Vulvar commissure	3
Vulvar introitus	2
Periclitoral	1
Perianal/anal	37
Perineum	10
Gluteal region	1
Anogenital, NOS	18
Unknown	9

NOS, not otherwise specified.

Light Microscopic Studies

The number of tissue blocks available for review varied from 1 to 3. The following histopathological features were assessed: connection of the lesion with a follicular infundibulum or with the overlying epidermis, ulceration of the overlying epidermis/epithelium, pseudocarcinomatous hyperplasia, prominent tumor necrosis, and cystic alteration.

For the epithelial and myoepithelial components, the following features were evaluated: metaplasia (oxyphilic, mucinous, and squamous), clear cell change of the luminal epithelial cells (so-called "lamprocytes") and myoepithelial cells, myoepithelial cell hyperplasia, presence of intraluminal macrophages, or deposits of calcium. Cases suspicious of mucinous metaplasia were stained with alcian blue and mucicarmine. When the above changes involved more than 25% of the neoplasm, they were referred to as prominent.

Mammary-type ductal changes including usual ductal hyperplasia and atypical ductal hyperplasia were defined according to Rosai.[14] Usual ductal hyperplasia was applied for an intraluminal proliferation of cells without atypia; some lesions show a solid pattern with "streaming" cellular growth pattern.[15] Atypical ductal hyperplasia was defined as a marked intraluminal proliferation of cuboidal epithelial cells with increased nuclear to cytoplasmic ratio, forming

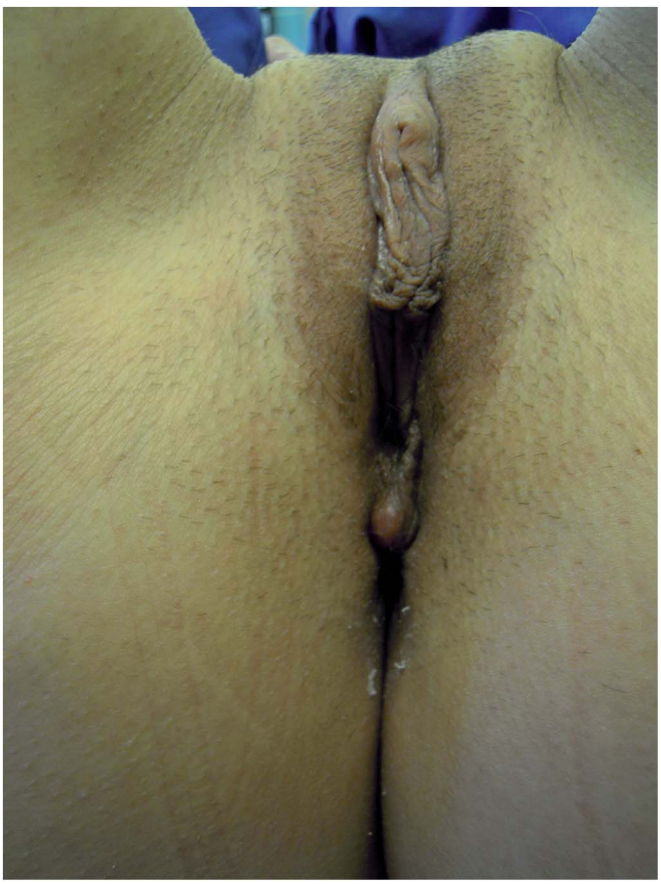

FIGURE 1. HP. A solitary nodule in the perianal area.

TABLE 3. Clinical Diagnoses (When Available) in HP

Clinical Diagnoses (n = 143)	No. Cases
Cyst	56
Fibroma	28
Atheroma	25
Lipoma	5
Verruca	4
Papilloma	3
Hidradenoma	3
Granuloma	2
Hemorrhoids	2
Polyp	2
Pyogenic granuloma	2
Vulvar cancer	2
Angiomyxoma	1
Apocrine gland carcinoma	1
Condyloma	1
Endometriosis	1
Fibrolipoma	1
Folliculitis	1
Hemangioma	1
Sebaceous cyst	1
Syringocystadenoma papilliferum	1

TABLE 4. Histopathological Features of HP

Histopathological Features (n = 264)	Frequency
Epithelial component changes	
Metaplasia	
Oxyphilic	95 (36%), prominent—10 (4%)
Squamous	3 (1%)
Mucinous	2 (<1%)
Mammary-type alterations	
Lamprocyte-like cells	3 (1%)
Usual ductal hyperplasia-like changes	60 (23%)
Atypical ductal hyperplasia-like changes	14 (5%)
Solid growth pattern	37 (14%)
Streaming growth pattern	22 (8%)
Adenosis-like changes	16 (6%)
Sclerosing adenosis-like changes	15 (6%)
Myoepithelial changes	
Clear cell change	45 (17%)
Hyperplasia	3 (1%)
Stromal component changes	
Sclerosis	37 (14%)
Focal hyperplasia of myofibroblast-like cells	6 (2%)
Foamy macrophages	18 (7%)
Calcium deposits	1 (<1%)
Giant cells	1 (<1%)
Other features	
Prominent cystic change	19 (7%)
Association with EMPD	2 (<1%)
Connection with the overlying epidermis (with/without plasma cell stromal infiltrate)	39/5 (15/2%)
Connection with follicular infundibulum (with/without plasma cell stromal infiltrate)	3/8 (1/3%)
Ulceration of the epidermis	14 (5%)
Pseudoepitheliomatous hyperplasia of the epidermis	1 (<1%)
Foamy macrophages within the lumina of the tubules	61 (23%)
Calcium within the lumina of the tubules	2 (<1%)
Tumor necrosis	6 (2%)
Remnants of AGMLG	72 (27%)
Normal	40 (56%)
Columnar cell change	27 (38%)
Columnar cell hyperplasia	13 (18%)
With surrounding inflammation	2 (3%)
Cystic change	1 (1%)

complex architectural patterns including micropapillae, true papillae, and cribriform spaces with Roman bridges, but with mild or no cytological atypia. Mammary-type adenosis-like changes were also recorded and whenever possible classified into sclerosing adenosis or other forms. Sclerosing adenosis was defined as a compact proliferation of small ductal structures with luminal epithelial cells, which are often atrophic and attenuated, have a preserved peripheral myoepithelial cell layer, and which lie in a sclerotic stroma.[16,17]

The following stromal features were evaluated: stromal sclerosis, focal hyperplasia of myofibroblast-like cells, the presence of foamy macrophages or giant cells, calcifications, and abundant plasma cells.

The presence of normal AGMLG remnants adjacent to the lesion was recorded, and also columnar cell change or columnar cell hyperplasia in these glands. Columnar cell change was defined as variably dilated lumina lined by 1–2 cell layers of elongated to ovoid columnar epithelial cells oriented perpendicularly to the basement membrane, having apical cytoplasmic blebs or snouts.[7] Columnar cell hyperplasia appeared as variably dilated lumina lined by more than 2 cell layers of elongated to ovoid columnar epithelial cells oriented perpendicularly to the basement membrane, having apical cytoplasmic blebs or snouts.[7]

Any other unusual features, if present, were also recorded. The size of the tumor was recorded in all patients either from medical charts or, when not available, measured on histopathological slides directly.

RESULTS

Clinical Data

All patients were women, whose ages at the time of diagnosis ranged from 25 to 82 years (median: 49 years; mean: 49.9 years) (Table 1). In 13 cases, the age of patients was unknown. The duration was known in 25 cases, ranging from 2 to 120 months (median: 12 months; mean: 22.8 months). In almost half of the patients (44%), the tumor had been present for less than 1 year. In all but 1 case, the lesions were solitary and occurred in the anogenital area (Fig. 1). One patient presented with 4 tumors. The location was unknown in 9 cases. Most involved the vulva (71.6%) and less frequently the perianal (14%) and perineal (3.8%) regions (Table 2). The neoplasms ranged in size from 2 to 20 mm in largest dimension (median: 7 mm; mean: 7.3 mm). The clinical diagnosis was suggested in 143 cases (Table 3); the most frequent diagnoses were a cyst (39.2%), fibroma (19.6%), atheroma (17.5%), lipoma (3.5%), and verruca (2.8%). None of these 143 lesions was suspected to be a HP.

Histopathological Data

All tumors had a similar microscopic appearance (Table 4). They were intradermal solid–cystic nodules with a complex pattern of branching and anastomosing tubules interconnected in a labyrinthine manner, with bands of fibrous tissue between them, focally forming papillae (Fig. 2A). The tubules and papillae were by a luminal layer of epithelial cells surrounded by a layer of myoepithelial cells. Decapitation secretion was a common feature. Nineteen cases (7.2%) were predominantly and markedly cystic (Fig. 2B). In 44 (16.7%) specimens, a connection with the overlying epidermis was noted and in the overwhelming majority of these (39/44, 89%), there was a dense plasma cell stromal infiltrate (Fig. 3A). Less frequently (11 cases, 4.2%), there was a connection with a follicular infundibulum (Fig. 3B). Ulceration of the epidermis

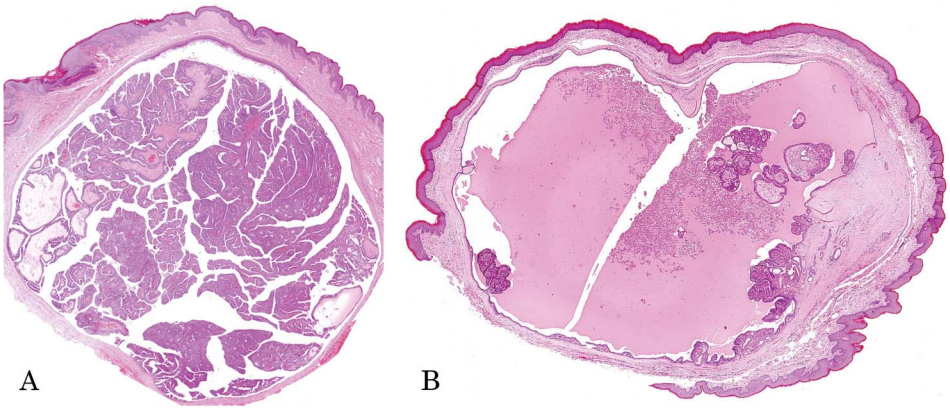

FIGURE 2. HP. Intradermal solid–cystic neoplasm with a complex pattern of branching and anastomosing tubules and papillae (A). Prominent cystic change (B).

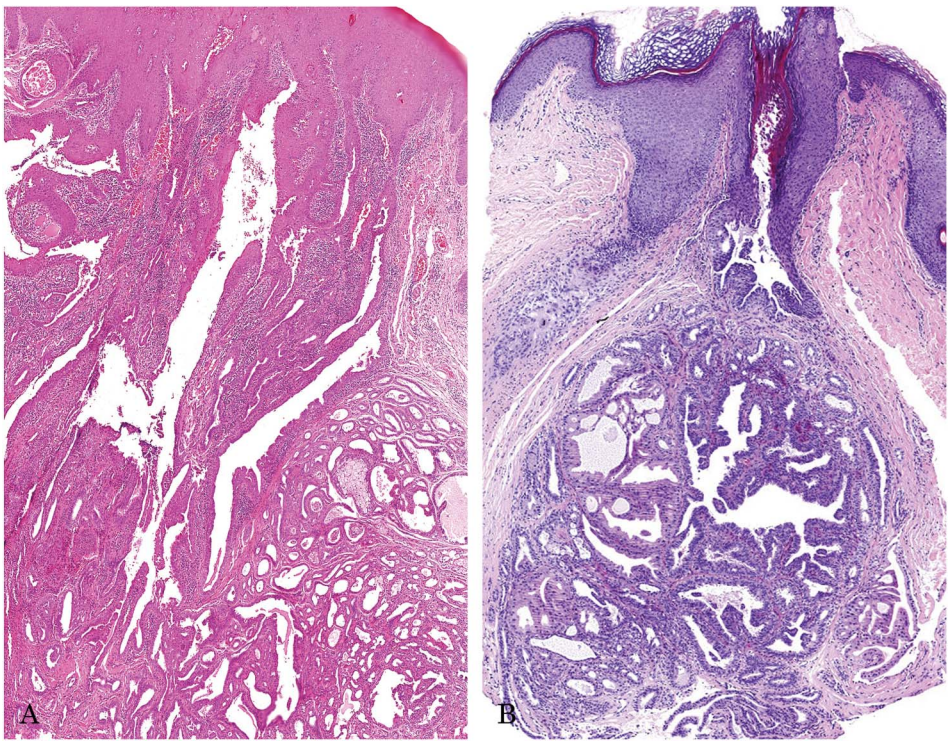

FIGURE 3. HP. Connection to the overlying epidermis. Note a plasma cell-rich infiltrate occasioning a resemblance to syringocystadenoma papilliferum (A). Connection to the follicular infundibulum (B).

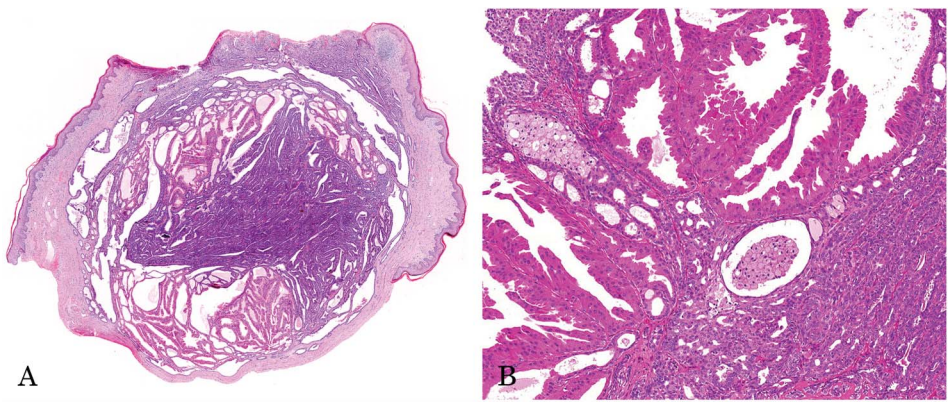

FIGURE 4. HP with oxyphilic metaplasia (A, B), streaming growth pattern and foamy macrophages within the lumina of the tubules (B). Note multiple areas with oxyphilic metaplasia (A).

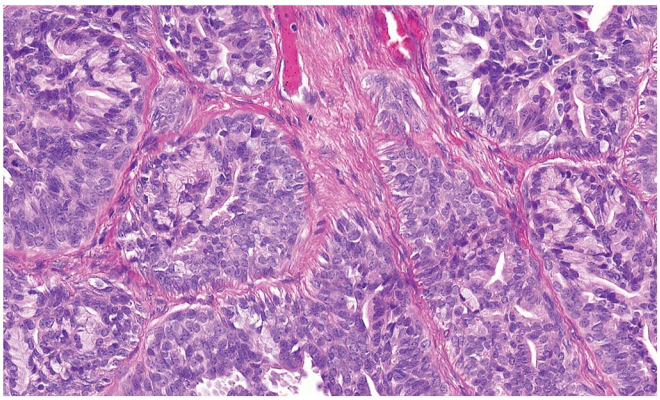

FIGURE 5. Mucinous metaplasia in HP.

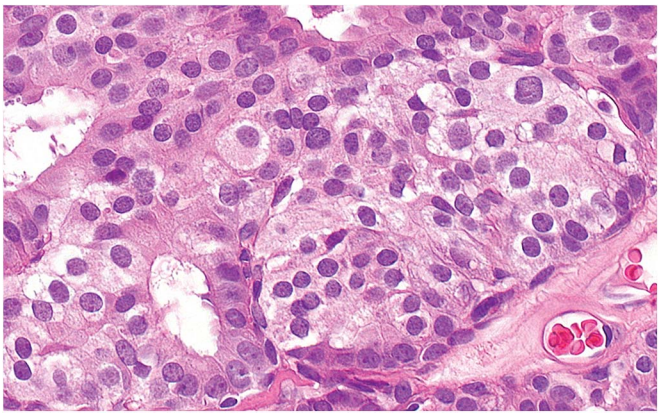

FIGURE 6. Clear cell change of the luminal epithelial cells.

was encountered in 14 cases (5.3%) and a single case manifested pseudoepitheliomatous hyperplasia. In 6 cases (2.3%), there was considerable necrosis.

The most common type of metaplasia of the epithelium was oxyphilic (Fig. 4A, B), which was usually multifocal and, in 10 cases (3.8%), it involved more than half of the lesion. The metaplastic cells had brightly eosinophilic cytoplasm, sometimes with discernable intracytoplasmic zymogen granules. Focally, these cells sometimes showed moderate cellular and nuclear pleomorphism with conspicuous nucleoli. Squamous and mucinous metaplasia (Fig. 5) were found only in 3 and 2 cases, respectively. The presence of intracellular mucin was confirmed by positive staining with alcian blue and mucicarmine. Three lesions exhibited clear cell change of the luminal epithelial cells (so-called lamprocytes—a rare benign finding in the breast described by Skorpil) (Fig. 6),[10] whereas focal clear cell change in the abluminal myoepithelial cells was a more common feature (17% of cases) (Fig. 7A, B).[10,18]

Fifteen (5.7%) HP showed changes resembling mammary sclerosing adenosis (Fig. 8A, B). So-called usual ductal hyperplasia was always a focal finding and occurred in 60 cases (22.7%) (Fig. 9A). In 36 cases with usual ductal hyperplasia, prominent intraluminal proliferation resulted in a focal solid growth pattern, with features of the so-called "streaming growth pattern" seen in mammary epitheliosis (as defined by Azzopardi) identified in 22 cases (Fig. 10).[15] Atypical ductal hyperplasia was observed in 14 cases (5.3%) (Fig. 9B).

With respect to changes in the stromal component, sclerosis was observed in 37 cases (14.0%), whereas focal hyperplasia of myofibroblast-like cells was seen in 6 cases (2.3%) (Fig. 11). The presence of foamy macrophages was not an uncommon finding; in 61 cases (23.1%), they were seen within the lumina of the tubules (Fig. 3A), and in 18 cases (6.8%), they were in the stroma.

Almost in a third of cases, remnants of AGMLG adjacent to the lesion were evident (Fig. 12A). In more than half of cases (40 cases), the epithelium lining these glands appeared normal; rarely, it manifested columnar cell change (27 cases) (Fig. 12B) or columnar cell hyperplasia (13 cases) (Fig. 12C). Occasionally, combinations of normal epithelium and columnar cell change were seen within 1 slide.

Two cases in our study were unusual in that they showed a combination of HP and extramammary Paget disease (EMPD), with large carcinoma cells having abundant pale cytoplasm infiltrating the overlying epidermis (Fig. 13).

DISCUSSION

HP is the most frequent benign neoplasm involving AGMLG. It was first described in 1878 by Werth.[19] Since that time, different authors have suggested various theories relating to pathogenesis and origins of the tumor, including sweat gland origin, association with, or resemblance to, the Wolffian apparatus, cystadenoma, and intraductal papilloma of the breast.[9,20] Van der Putte proposed the existence of AGMLG as a normal constituent of the anogenital area, in contrast to the traditional view that these represented ectopic breast

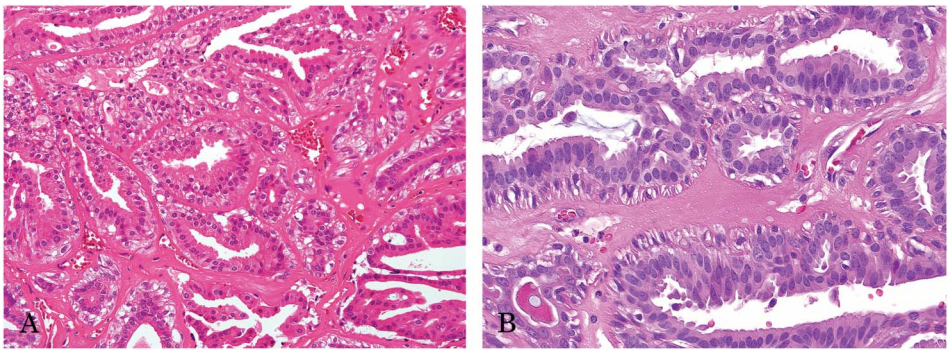

FIGURE 7. Clear cell change of the abluminal myoepithelial cells (A, B).

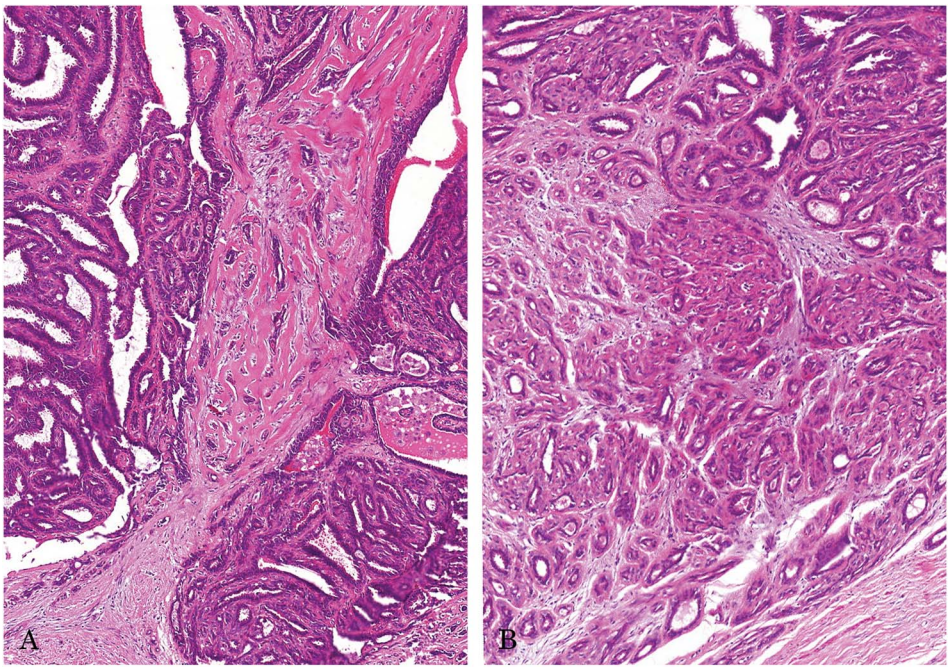

FIGURE 8. Sclerosing adenosis in HP (A, B).

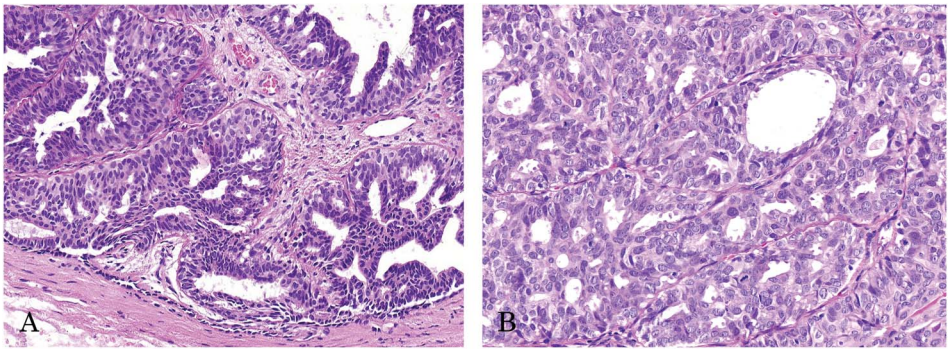

FIGURE 9. HP with usual (A) and atypical (B) ductal hyperplasia.

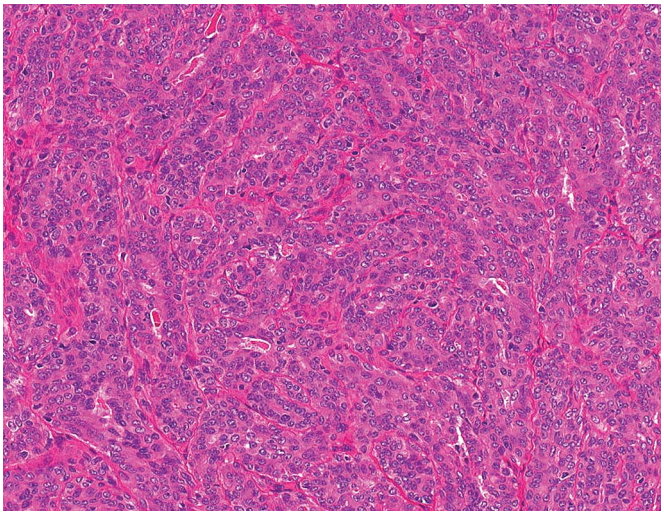

FIGURE 10. HP with solid and streaming growth pattern.

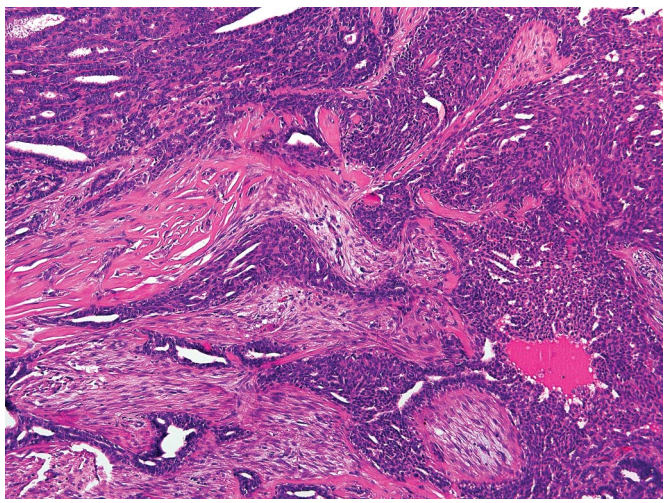

FIGURE 11. HP with a prominent hyperplasia of stromal myofibroblast-like cells.

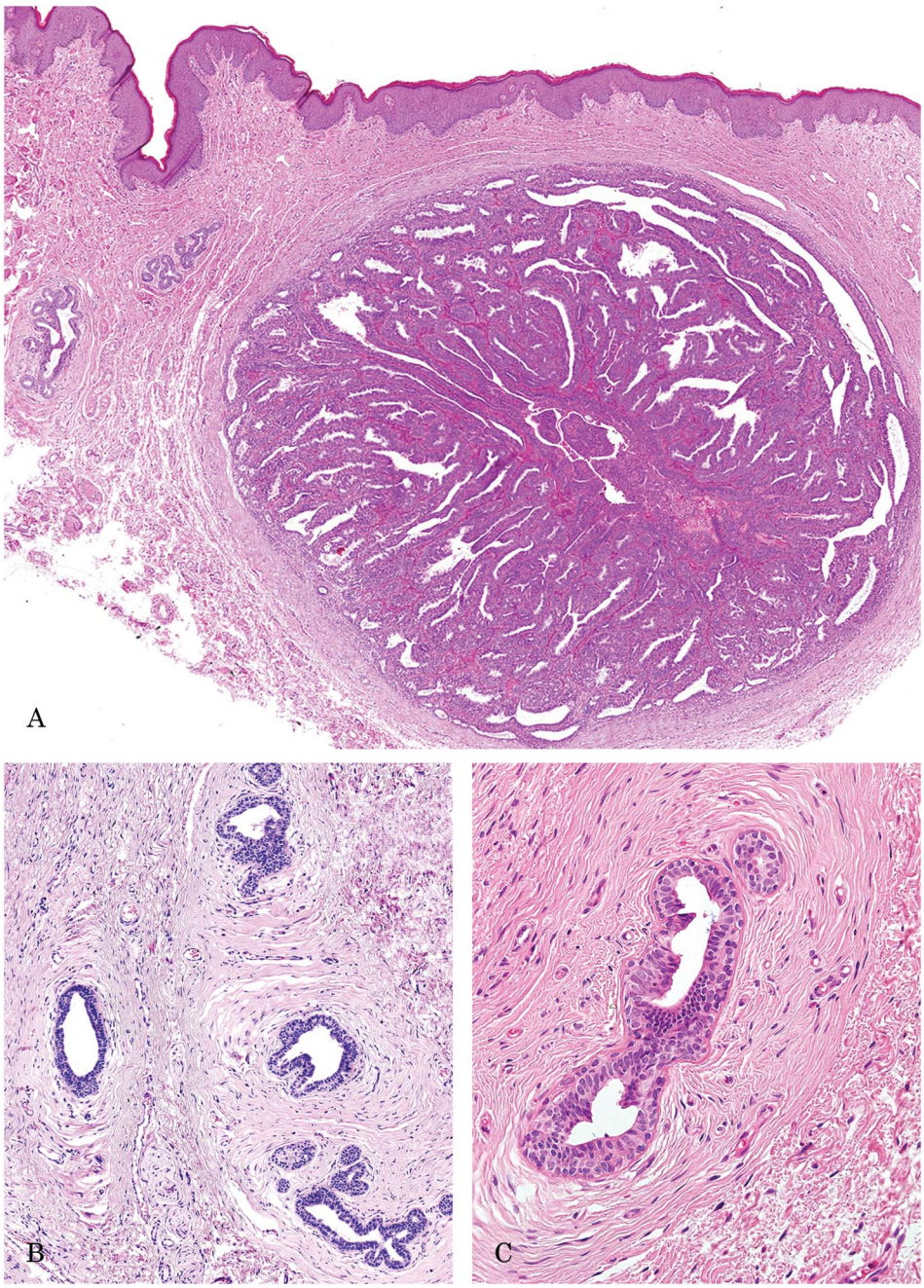

FIGURE 12. HP with adjacent remnants of AGMLG, a feature recognized in a third of cases (A). Columnar cell change (B) and columnar cell hyperplasia (C) in the epithelium lining these glands.

tissue.[1–5] This origin of HP explains its resemblance to mammary intraductal papilloma. Hormonal influences and a role for the human papillomavirus (HPV) in the etiology of disease have been suggested, but HPV is detected only in a minority of cases, suggesting that HPV has an unlikely causal role.[10,21]

In our study, in almost one-third of cases, we noticed the presence of AGMLG remnants adjacent to the lesion, strongly suggesting a histopathogenetic association of HP with AGMLG. The epithelium lining these glands appeared normal (56%) or manifested alterations compatible with columnar cell change (38%) or columnar cell hyperplasia (18%) as defined in breast pathology. Sometimes normal epithelium and columnar cell change/hyperplasia coexisted.

We and others have shown that HP is characterized by great cytoarchitectural variability, sometimes within the same tumor.[7,9,10,12,20] In this study, some tumors were essentially solid and composed of papillary and tubular areas, whereas others were predominantly cystic lesions. Both locations within a large cystic duct and massive necrosis are seen sometimes in breast intraductal papilloma.[14,22] In addition, we observed a range of other morphological features analogous to those occurring in benign breast disease. These included sclerosing adenosis-like changes, atypical and usual ductal

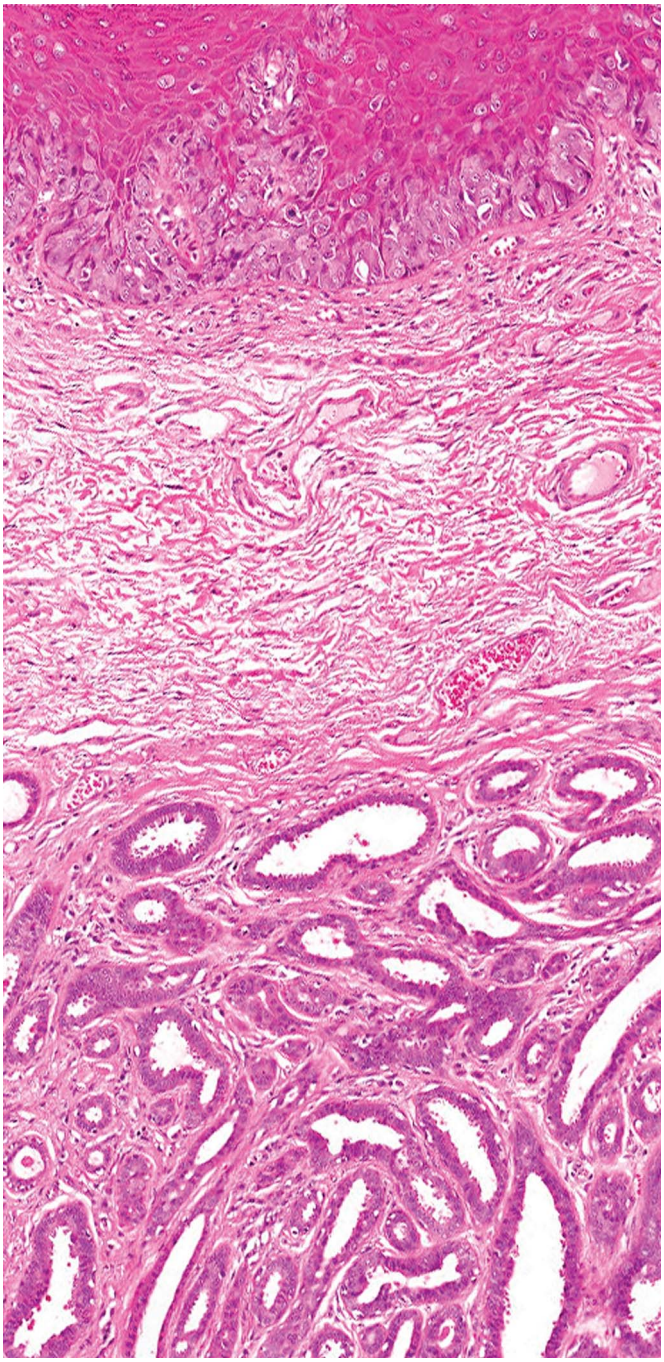

FIGURE 13. HP associated with EMPD. Note the intraepidermal carcinoma cells above the HP.

hyperplasia and solid and streaming growth patterns. These features may impart unusual appearances and should not be misinterpreted as malignant. The recognition of myoepithelial cells in areas of solid growth aid in the distinction from invasive carcinoma.[10]

Some HP have a connection to the epidermis or follicular infundibulum, often accompanied by a subepidermal plasma cell infiltrate, thus occasioning a resemblance to syringocystadenoma papilliferum.[23–25] In fact, some reported cases of syringocystadenoma papilliferum in the anogenital area likely represent this occurrence.

The most common type of metaplasia of the epithelium was oxyphilic. The exact nature of this change remains unknown.[10] It can occur due to a plethora of nonribosomal cytoplasmic organelles.[26] The term "apocrine metaplasia" is used for such changes in breast pathology, but we prefer oxyphilic as HP manifests apocrine differentiation, so the term apocrine metaplasia would be an oxymoron. Besides occurring in intraductal papilloma, oxyphilic metaplasia is most frequently observed in the epithelium of simple cysts and hyperplastic ducts, in sclerosing adenosis, fibroadenomas, and other benign epithelial proliferations, both in orthotopic breast and in lesions of AGMLG.[10,14] Sometimes these cells show moderate cellular and nuclear pleomorphism consistent with apocrine adenosis. It is important not to confuse this change, especially in areas of solid growth, with adenocarcinoma.[7]

Squamous metaplasia was a rare finding in our and other studies.[9] This change also can be seen in breast intraductal papilloma.[22,27] The presence of an extensive squamous component in a mammary lesion should raise the suspicion of malignancy.[14] The rarest cell types, as found by others,[12] were mucinous and clear cells, the latter being a degenerative phenomenon.[12,28] Clear epithelial cells can be found in breast lesions and sometime are termed lamprocytes.[10] Rarely, clear cells can imitate sebocytes as in a case of intraductal papilloma.[27] Clear cell change involving myoepithelial cells proved to be a more frequent feature (17% of cases).

The presence of foamy macrophages in HP was not an uncommon finding, occurring within the lumina of the tubules (23%) and in the stroma (7%). Such cells, with a centrally located nucleus and a markedly vacuolated cytoplasm, morphologically resembled sebaceous cells.[29,30] With respect to the breast, Damiani et al[31] reported similar stromal and intraluminal foamy cells in 50 benign breast lesions. HP also can be a part of complex neoplastic lesions involving AGMLG. Two cases with mixed histopathological features of fibroadenoma and HP and pseudoangiomatous stromal hyperplasia have been reported.[32,33]

HP can rarely be seen in association with different benign and malignant diseases, including Bartholin gland abscess,[34] melanoma,[35] and squamous cell carcinoma.[36] An extremely rare occurrence is concomitant presentation of EMPD and HP, previously reported twice.[35,37] In our study 2 cases showed a combination of HP and EMPD. In 1 case, HP was present beneath the intraepidermal areas affected by the EMPD, whereas in the second case, HP and EMPD were present in different blocks. The differential diagnosis for the latter instance is Toker cell hyperplasia. Clear cells of Toker (intraepithelial cells found in normal nipples and in association with AGMLG of the vulva as a normal constituent of genital skin) have been hypothesized to be a precursor of both mammary and EMPD some cases.[5–8,38] Toker cell hyperplasia has been described both in breast and in extramammary locations. However, there are no strict criteria for distinguishing Toker cell hyperplasia

and incipient EMPD.[39,40] In our cases, the diagnosis of EMPD did not pose a problem, as there were large carcinoma cells having abundant pale cytoplasm infiltrating the epidermis along the affected areas.

The clinical data of patients from our study in terms of the age, location, clinical presentation, duration of the disease, and size of the lesion corroborate the previously published data[9,12,20,28] HP affects almost always white women.[9,12,20,28,41] Only a single case of anogenital (perianal) HP has been described in a male.[42] All but 1 HP in our series were solitary and small. Only 1 woman presented with 4 lesions involving both labia majora. Multiple HP have been described but are rare. Woodworth et al[20] reported 3 patients who had multiple vulvar HP, 1 patient having 3 lesions, and 2 patients each having 2 lesions. Meeker et al[9] also reported 2 patients each having 2 tumors. Also rare are reports of lesions exceeding 2 cm.[43,44]

HP is a benign lesion with good prognosis. The mitotic index in these lesions can be often high (up to 13/10 high-power field), but it does not predict a more aggressive outcome.[11] In most of the cases, only surgical removal is required to cure the patient.[41] Because of the recognized benignity of the lesions, no follow-up was obtained.

In conclusion, we present the largest series of HP, detailing a wide spectrum of morphological changes that may occur in these lesions and adjacent AGMLG, analogous to those occurring in breast and benign breast conditions. Some changes may impart unusual histological appearances and thus represent a diagnostic pitfall; however, keeping in mind, analogies with breast pathology will aid in the correct interpretation of the alterations.

REFERENCES

1. van der Putte SC. Anogenital "sweat" glands. Histology and pathology of a gland that may mimic mammary glands. *Am J Dermatopathol.* 1991; 13:557–567.
2. Van der Putte SC. Ultrastructure of the human anogenital "sweat" gland. *Anat Rec.* 1993;235:583–590.
3. van der Putte SC. Mammary–like glands of the vulva and their disorders. *Int J Gynecol Pathol.* 1994;13:150–160.
4. van der Putte SC, van Gorp LH. Cysts of mammarylike glands in the vulva. *Int J Gynecol Pathol.* 1995;14:184–188.
5. van der Putte SC. Clear cells of Toker in the developing anogenital region of male and female fetuses. *Am J Dermatopathol.* 2011;33:811–818.
6. Belousova IE, Kazakov DV, Michal M, et al. Vulvar toker cells: the long–awaited missing link: a proposal for an origin–based histogenetic classification of extramammary paget disease. *Am J Dermatopathol.* 2006;28:84–86.
7. Kazakov DV, Spagnolo DV, Kacerovska D, et al. Lesions of anogenital mammary–like glands: an update. *Adv Anat Pathol.* 2011;18:1–28.
8. Willman JH, Golitz LE, Fitzpatrick JE. Vulvar clear cells of Toker: precursors of extramammary Paget's disease. *Am J Dermatopathol.* 2005;27:185–188.
9. Meeker JH, Neubecker RD, Helwig EB. Hidradenoma papilliferum. *Am J Clin Pathol.* 1962;37:182–195.
10. Kazakov DV, Mikyskova I, Kutzner H, et al. Hidradenoma papilliferum with oxyphilic metaplasia: a clinicopathological study of 18 cases, including detection of human papillomavirus. *Am J Dermatopathol.* 2005;27:102–110.
11. Sington J, Chandrapala R, Manek S, et al. Mitotic count is not predictive of clinical behavior in hidradenoma papilliferum of the vulva: a clinicopathologic study of 19 cases. *Am J Dermatopathol.* 2006;28: 322–326.
12. Scurry J, van der Putte SC, Pyman J, et al. Mammary–like gland adenoma of the vulva: review of 46 cases. *Pathology*. 2009;41: 372–378.
13. Vazmitel M, Spagnolo DV, Nemcova J, et al. Hidradenoma papilliferum with a ductal carcinoma in situ component: case report and review of the literature. *Am J Dermatopathol.* 2008;30:392–394.
14. Rosai J. *Rosai and Ackerman's Surgical Pathology*. Toronto, Canada: Elsevier Inc; 2004.
15. Azzopardi JG, Ahmed A, Millis RR. *Problems in Breast Pathology*. Azzopardi AG, ed. London, Philadelphia: WB Saunders; 1979.
16. Rosen P. *Rosen's Breast Pathology*. Philadelphia, PA: Lippincot Williams and Wilkins; 2009.
17. Tavassoli FA, Devilee P, eds. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs*. Lyon, France: IARCPress; 2003.
18. Bussolati G. Clear cell metaplasia of the breast. *Histopathology*. 1990;16: 316.
19. Werth R. Anatomy of cysts of the vulva. *Zentralbl Gynakol.* 1878; 22:513–516.
20. Woodworth H Jr, Dockerty MB, Wilson RB, et al. Papillary hidradenoma of the vulva: a clinicopathologic study of 69 cases. *Am J Obstet Gynecol.* 1971;110:501–508.
21. Kazakov DV, Nemcova J, Mikyskova I, et al. Human papillomavirus in lesions of anogenital mammary–like glands. *Int J Gynecol Pathol.* 2007; 26:475–480.
22. Flint A, Oberman HA. Infarction and squamous metaplasia of intraductal papilloma: a benign breast lesion that may simulate carcinoma. *Hum Pathol.* 1984;15:764–767.
23. Nishie W, Sawamura D, Mayuzumi M, et al. Hidradenoma papilliferum with mixed histopathologic features of syringocystadenoma papilliferum and anogenital mammary-like glands. *J Cutan Pathol.* 2004;31:561–564.
24. Parks A, Branch KD, Metcalf J, et al. Hidradenoma papilliferum with mixed histopathologic features of syringocystadenoma papilliferum and anogenital mammary-like glands: report of a case and review of the literature. *Am J Dermatopathol.* 2012;34:104–109.
25. Stewart CJ. Syringocystadenoma papilliferum-like lesion of the vulva. *Pathology*. 2008;40:638–639.
26. Chang A, Harawi SJ. Oncocytes, oncocytosis, and oncocytic tumors. *Pathol Annu.* 1992;27:263–304.
27. Jiao YF, Nakamura S, Oikawa T, et al. Sebaceous gland metaplasia in intraductal papilloma of the breast. *Virchows Arch.* 2001;438:505–508.
28. Ioannides G. Hidradenoma papilliferum. *Am J Obstet Gynecol.* 1966;94: 849–853.
29. Minami S, Sadanobu N, Ito T, et al. Non-anogenital (ectopic) hidradenoma papilliferum with sebaceous differentiation: a case report and review of reported cases. *J Dermatol.* 2006;33:256–259.
30. Teloh HA. Apocrine adenoma of the anus. *Cancer*. 1954;7:367–372.
31. Damiani S, Cattani MG, Buonamici L, et al. Mammary foam cells. Characterization by immunohistochemistry and in situ hybridization. *Virchows Arch.* 1998;432:433–440.
32. Konstantinova AM, Kacerovska D, Michal M, et al. A composite neoplastic lesion of the vulva with mixed features of fibroadenoma and hidradenoma papilliferum combined with pseudoangiomatous stromal hyperplasia containing multinucleated giant cells. *Am J Dermatopathol.* 2014;36:e171–174.
33. Vazmitel M, Pavlovsky M, Kacerovska D, et al. Pseudoangiomatous stromal hyperplasia in a complex neoplastic lesion involving anogenital mammary–like glands. *J Cutan Pathol.* 2009;36:1117–1120.
34. Docimo S Jr, Shon W, Elkowitz DE. Bartholin's abscess arising within hidradenoma papilliferum of the vulva: a case report. *Cases J.* 2008;1:282.
35. Simpson WA, Burke M, Frappell J, et al. Paget's disease, melanocytic neoplasia and hidradenoma papilliferum of the vulva. *Histopathology*. 1988;12:675–679.
36. Barre C, Lorenzato M, Bourdat B, et al. Vulvar invasive squamous cell carcinoma and hidradenoma papilliferum. Case report [in French]. *Gynecol Obstet Fertil.* 2007;35:776–779.
37. Stefanato CM, Finn R, Bhawan J. Extramammary Paget disease with underlying hidradenoma papilliferum: guilt by association? *Am J Dermatopathol.* 2000;22:439–442.
38. Toker C. Clear cells of the nipple epidermis. *Cancer*. 1970;25:601–610.

39. Decaussin M, Laville M, Mathevet P, et al. Paget's disease versus Toker cell hyperplasia in a supernumerary nipple. *Virchows Arch.* 1998;432: 289–291.
40. van der Putte SC, Toonstra J, Hennipman A. Mammary Paget's disease confined to the areola and associated with multifocal Toker cell hyperplasia. *Am J Dermatopathol.* 1995;17:487–493.
41. Virgili A, Marzola A, Corazza M. Vulvar hidradenoma papilliferum. A review of 10.5 years' experience. *J Reprod Med.* 2000;45:616–618.
42. Loane J, Kealy WF, Mulcahy G. Perianal hidradenoma papilliferum occurring in a male: a case report. *Ir J Med Sci.* 1998;167:26–27.
43. Veraldi S, Schianchi-Veraldi R, Marini D. Hidradenoma papilliferum of the vulva: report of a case characterized by unusual clinical behavior. *J Dermatol Surg Oncol.* 1990;16:674–676.
44. Duhan N, Kalra R, Singh S, et al. Hidradenoma papilliferum of the vulva: case report and review of literature. *Arch Gynecol Obstet.* 2011;284: 1015–1017.